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Review

Bone and calcium metabolism and antiepileptic drugs

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ABSTRACT

There is increasing evidence suggesting that epilepsy and its treatment can affect bone mineralization and calcium metabolism. Many studies have shown a significant reduction in bone mineral density in patients treated with classic (phenobarbital, carbamazepine, valproate, etc.) and with new (oxcarbazepine, gabapentin) antiepileptic drugs. In spite of data about the possible effects of the antiepileptic drugs on calcium metabolism, the mechanisms of this important side effect remain to be defined. The abnormalities of calcium metabolism were thought to result from the cytochrome P450 enzyme-inducing properties of some antiepileptic drugs and the resultant reduction in vitamin D levels, but the effect of many medications (e.g., valproate) cannot be readily explained by vitamin D metabolism.

In this article, the literature related to the effects of classic and new antiepileptic drugs on bone health and calcium metabolism is reviewed.

Contents

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1. Introduction

The adverse effects of antiepileptic drugs (AEDs) on bone health were first reported nearly four decades ago, and, since then, a growing body of literature indicates that patients taking AEDs are at increased risk for low bone mineral density and metabolic bone disease including changes in bone turnover, osteoporosis, alterations in bone quality, and, most importantly, fracture.

First of all, it can be useful to focus on the basic bone physiology. Maintenance of optimal bone health depends on an adequate supply of calcium and on the effects of some hormones. Parathyroid hormone (PTH) is a peptide hormone that can alter serum calcium via actions on three target organs: bone, intestinal mucosa and kidney. PTH increases bone turnover and causes loss of calcium from bone through increases in osteoclast number and activity. This hormone also increases intestinal calcium absorption and acts in the kidney on the distal tubule to promote calcium reabsorption and on the proximal tubule to decrease phosphate absorption.

Vitamin D is metabolized in the liver to 25-hydroxyvitamin D (25OHD), which is in turn metabolized in the kidney to 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D), the biologically active form. Drugs that increase liver hydroxylases can reduce the amount of 25OHD. 1,25-$(OH)_2$D synthesis is stimulated by hypocalcemia, PTH and hypophosphataemia. Vitamin D stimulates intestinal calcium absorption and promotes mineralization of the skeleton.

Bone remodeling is a lifelong process by which skeleton is being continuously resorbed and replaced to maintain skeletal integrity; serum markers of bone formation are serum bone specific alkaline phosphatase (bALP), osteocalcin (OC), carboxy-terminal propeptide of type I procollagen (PICP), amino-terminal propeptide of type III procollagen (PIIINP), and markers of bone resorption are serum carboxy-terminal telopeptide of type 1 collagen (ICTP) and urinary N-telopeptide of type 1 collagen bone (NTx).

Several studies which assessed bone metabolism status and bone mineral density (BMD) in adults and children on AEDs have shown rather controversial results.

This review analyzes the main data of literature in order to summarize the principal side adverse effects on bone induced by the most frequently used AEDs.

2. Classic antiepileptic drugs

2.1. Benzodiazepines

The most common benzodiazepines (BZP) used are clonazepam, diazepam and lorazepam. These are distinct allosteric binding sites on the GABAa receptor chloride ionophore to enhance GABA-mediated increases in chloride conductances [1–3].

Some studies have demonstrated a limited increase in the risk of fractures, even at very low doses, for several types of BZPs. There was a trend toward increasing fracture risk with increasing dose [8–10], especially in the spine [8]. Also, a trend toward higher fracture risk was seen with increasing half-life of the drugs. BZPs with a shorter half-life may thus be preferred to reduce the risk of fractures, but it should be noted that lower half-life may not completely abolish the increased risk of fractures, although the relative risk is rather limited [9].

A few studies investigate effects of BZP on bone metabolism. Kulak et al. evaluating 58 young adults with epilepsy on chronic AEDs therapy, have demonstrated significant abnormalities of bone metabolism, characterized by reduced BMD, reduced 25OHD and increased alkaline phosphatase (ALP). Mean results of routine biochemical testing, such as total calcium (Ca), phosphorus (P), magnesium and PTH, were normal and did not differ statistically [4]. Similarly, Farhat et al. have determined the effect of AED on vitamin D levels and bone density in ambulatory patients and to compare the effects of enzyme-inducing and noninducing AED (such clonazepam) of single vs. multiple therapy on bone density. No significant difference in 25OHD levels was observed between patients on enzyme-inducing and noninducing AED. In this study a significant proportion (>50%) of patients in both age groups had low 25OHD levels and low BMD in adults of both sexes, independent of vitamin D levels [5]. In contrast, in another study, BZPs did not seem to have an effect on BMD [6] and thus did not induce the modest increase in fracture risk observed in a prior study [7]. In conclusion, BZP can adversely affect bone health with a consequent risk of fractures.

2.2. Carbamazepine

Carbamazepine (CBZ) is one of the front line AEDs for treatment of partial seizures as well as secondary generalized seizures in adults and children. It mainly acts on voltage-gated sodium channels that are stabilized in their inactivated state [11,12].

2.3. CBZ and BMD

Several studies on adults and children have shown that CBZ treatment induces a state of decreased BMD in the lumbar spine [5,13–19], femoral neck [5,19–21], forearm [19,22] and calcaneus [23], but there have been some conflicting results, especially in children.

Two recent studies by Kumandas et al. [15] and Kim et al. [23] showed that the decrease in BMD was related to reduced levels of vitamin D secondary to the property of the drug to activate specific cytochrome P450 (CYP-450) isoenzymes, which are involved in vitamin D catabolism [24].

The work by Kumandas et al. was a cross-sectional, retrospective study that examined the effects of at least 2 years of CBZ therapy on bone mineral density in 33 preadolescent patients. They showed that these patients had reduced BMD in the lumbar spine [15].

The report by Kim et al. was a longitudinal study that showed a significant reduction in BMD in the right calcaneus in 10 adult patients after 6 months of CBZ monotherapy [23]. In both studies, reduced BMD was associated with lower levels of 25(OH)D.

In contrast, 6 other cross-sectional studies [5,14,16,19,20,25] and 2 longitudinal studies [13,21] have demonstrated a lack of correlation between serum levels of vitamin D and reduced BMD, suggesting that the loss of bone mass observed in patients treated with CBZ may not be explained by an effect of drug on vitamin D metabolism. Rather, it may be due at least in part to direct effects of CBZ on bone cell proliferation, leading to reduced growth of human bone cells [20,26]. Among these studies, the largest and most recent was a study by El-Hajj Fuleihan et al. [19], who studied 225 ambulatory patients (137 adults and 88 children) treated with different AEDs, including CBZ monotherapy. The results indicated that the adult patients on enzyme-inducing drugs such as CBZ tended to have lower BMD in the lumbar spine and total hip compared to those on noninducers; BMD was negatively correlated with the duration of treatment in adults and with polytherapy in children.

In agreement with these results, 2 previous studies [5,20] demonstrated that the duration of CBZ therapy is an independent predictor of BMD in adults.

Gender differences in the effects of CBZ on bone mineral density have been analyzed. In several studies, the effect was more marked in female patients [27–29]. In contrast, 2 studies [14,21] showed that the incidence of osteopenia was significantly greater in males than in females. Other studies did not show a sex-related difference [13,19,23].